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EXAMINER	
SWOPE, SHERIDAN	

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/677,734	GARDNER ET AL.	
	Examiner	Art Unit	
	Sheridan L. Swope	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *June 13, 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *2,3,5,10 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☒ Claim(s) *1,4,6-9,11-14 and 16-20* is/are objected to.

8)☒ Claim(s) *1,4,6-9,11-14 and 16-20* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Exhibit A*.

DETAILED ACTION

Applicant's election with traverse of Invention III, Claims 4, 9, and 14, as well as the PAS kinase (A) and host cell (G), in their response of June 13, 2005 is acknowledged.

The traversal is on the following grounds. (i) The Groups are all directed to the same method of changing binding specificity of a PAS domain by introducing into the hydrophobic core of the PAS domain a foreign ligand and (b) detecting a resultant change in the functional surface binding specificity of the PAS domain. (ii) The action incorporates canned sentences citing search burden, different steps, and different results but makes no specific analysis of findings relevant to our claims.

These arguments are not found to be persuasive. Applicants seem to be discussing the Restriction/Election requirement in terms of Lack of Unity i.e., that a special technical feature linking the claims is that the all relate to "the same method of changing binding specificity of a PAS domain". However, the instant application is not a US 371 filing of a PCT application; therefore, US Restriction/Election practice has been used. 35 U.S.C. 121 allows restriction of inventions which are independent or distinct. Each of the methods of Inventions I-VI are distinct in the steps they comprise, the products used to perform the methods, and/or the result produced. Invention I is drawn to a method of changing the intermolecular binding of a PAS-containing protein, Invention II is drawn to a method of changing the intramolecular binding of a PAS domain-containing protein, Invention III is drawn to a method of changing the kinase activity of a PAS domain-containing protein, Invention IV is drawn to a method of changing the kinase specificity of a PAS domain-containing protein, Invention V is drawn to a method of changing the channel patency of a PAS domain-containing protein, and Invention VI is drawn to

a method of changing the channel specificity of a PAS domain-containing protein. It would be obvious to a person of ordinary skill in the art that each of these inventions, at the least, produce different effects. In addition, it is obvious that the methods of Inventions (A)-(H) use different products.

It is acknowledged that the Examiner used "canned" sentences in the Restriction/Election requirement. Nonetheless, said "canned" sentences convey an accurate analysis of the reasons for restriction.

The requirement is still deemed proper and is therefore made FINAL.

It is acknowledged that Applicants have added Claims 16-20. Claims 1-20 are pending. Claims 16 and 19 are deemed to be linking claims, which link Inventions I-VI. Claims 2, 3, 5, 10, and 15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected Inventions, there being no allowable generic or linking claim. Claims 4, 9, 14, 17, 18, and 20 as well as linking Claims 1, 6-8, 11-13, 16, and 19, in so far as they recite the elected invention, are examined on their merits.

Specification-Objections

The specification is objected to for the following reasons.

On page 4, lines 18-20, the specification appears to be missing an article as indicated:

> In contrast, AHR PAS-B binds both HSP90, a common chaperone of unfolded proteins, and ligand, and **[the]** AHR PAS-B domain is unfolded without ligand (e.g. Kikuchi, et al., 2003, J Biochem 134, 83-90).

On page 14, line 9, the specification uses an undefined abbreviation, "KIX".

On page 14, line 25, and elsewhere throughout the specification, a reference "Hajduk et al, 1997" is cited. The list of citations discloses two references for Hajduk et al that are

published in 1997. The specification should be amended to, in each instance, refer to a single citation published by Hajduk et al in 1997.

On page 15, lines 25-26, the specification states that Rutter et al, 2001 teaches that PAS kinase regulates sugar metabolism. Rutter et al, 2001 do not disclose said teachings.

On page 15, line 31, "later" should be "latter".

On page 16, lines 1-2, the phrase "inform the mode of kinase regulation by the PAS domain" is not proper English.

Title

The title is objected to for not being descriptive of the instant invention, which is a method.

Description of the Drawings

The legend for Figure 3B is objected to for not describing the right-hand panel.

Abstract

The abstract is objected to for being two paragraphs. Applicant is reminded of the proper language and format for an abstract of the disclosure.

> The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

Claims-Objections

Claims 4, 6-9, 11-14, and 16-20 are objected to for improper antecedent usage. In each said claim, the phrase "A method according to claim #" should be amended to "The method

according to claim #". For example, in Claim 4 "A method according to claim 1" should be amended to "The method according to claim 1".

Claim 7 is objected to for "the host", which has no antecedent basis.

Claims 1, 4, 6-9, 11-14, and 16-20 are objected to for reciting non-elected subject matter.

Claims 19 and 20 are objected to for "part of PAS kinase", which would be more clearly stated as "a fragment of PAS kinase".

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Double Patenting

> The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
> A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).
> Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Claims 1, 4, 11, 12, 16, 17, 19, and 20 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 11 of US Patent 6,319,679. Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 1, 4, 11, 12, 16, 17, 19, and 20 herein and Claim 11 of US Patent 6,319,679 are both directed to methods for detecting the effect of binding ligand on the kinase activity of PAS kinase. The claims differ in that the method of Claim 11 of US Patent 6,319,679 encompasses determining the effect of ligand binding to regions of PAS kinase other than the hydrophobic core of the PAS domain also, while Claims 1, 4, 11, 12, 16, 17, 19, and 20 herein recite a method for determining the effect of ligand binding to the hydrophobic core of the PAS kinase PAS domain. The portion of the specification in 6,319,679 that supports the recited methods includes embodiments that would anticipate Claims 1, 4, 11, 12, 16, 17, 19, and 20 herein, e.g., a method for determining the effect on kinase activity of ligand binding to the hydrophobic core of the PAS kinase PAS domain, which are also the methods specifically recited in Claim 11 of US Patent 6,319,679 (col 15, line 61- col 16, line 67). Claims 1, 4, 11, 12, 16, 17, 19, and 20 herein cannot be considered patentably distinct over Claim 11 of US Patent 6,319,679 when there are specifically recited embodiments (a method for determining the effect on kinase activity of ligand binding to the hydrophobic core of the PAS kinase PAS domain) that would anticipate Claims 1, 4, 11, 12, 16, 17, 19, and 20 herein. Alternatively, Claims 1, 4, 11, 12, 16, 17, 19, and 20 herein cannot be considered patentably distinct over Claim 11 of US Patent 6,319,679 when there are specifically disclosed embodiments in 6,319,679 that supports Claim 11 of that patent and falls within the scope of Claims 1, 4, 11, 12, 16, 17, 19, and 20 herein, because it would have been obvious to a skilled artisan to modify the methods of Claim 11 of US Patent 6,319,679 by

selecting a specifically disclosed embodiment that supports those claims, i.e., a method for determining the effect on kinase activity of ligand binding to the hydrophobic core of the PAS kinase PAS domain, as disclosed in 6,319,679. One having ordinary skill in the art would have been motivated to do this, because such an embodiment, is disclosed as being a preferred embodiment within Claim 11 of the prior patent.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4, 6-9, 11-14, and 16-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the following reasons.

Claim 1 uses the phrase "wherein the PAS domain is predetermined, prefolded...". Neither the claims nor the specification define "predetermined" or "prefolded" and a person of ordinary skill in the art would not know the metes and bounds of the recited invention. Therefore, Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite. Claims 4, 6-9, 11-14, and 16-20 as dependent from Claim 1, are rejected under 35 U.S.C. 112, second paragraph, for the same reasons.

Claim 9 recites a method of using a host cell for measuring the effect on a cellular process of ligand binding to the hydrophobic core of a PAS domain. Claim 9, as written, is dependent from Claim 1, which recites an in vitro biochemical assay. Thus, Claim 9 fails to be encompassed by the method Claim 1 or to further limit of Claim 1. Claim 9 is indefinite and confusing because the recited method cannot be a cellular method using a host cell and, at the

same time, be an in vitro method using purified kinase. A person of ordinary skill in the art would not know the metes and bounds of the recited invention. Claims 14 and 18, as dependent from Claim 9, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the same reasons.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

In this regard, the application disclosure and claims are compared per the factors indicated in the decision In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but are not limited to: (1) the nature of the invention; (2) the breath of the claims; (3) the predictability or unpredictability of the art; (4) the amount of direction or guidance presented; (5) the presence or absence of working examples; (6) the quantity of experimentation necessary; (7) the relative skill of those skilled in the art. Each factor is here addressed on the basis of a comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation.

Not all pas proteins or all pas kinases.

Claims 1, 4, 6-9, 11-14, and 16-20 are rejected under 35 U.S.C. 112, first paragraph, for lack of enablement. The specification is enabling for using the PAS kinase, as set forth by

GenBank Accession No. AF387103, for testing the effect of ligand binding to the hydrophobic core of the PAS domain on (i) kinase activity using the method of Rutter et al, 2001 (Figs 3 & 4) and (ii) on glycogen synthase activity using the method of Rutter et al, 2002 (Fig 7). However the specification does not reasonably provide enablement for testing the effect of any ligand on the kinase activity of any protein having a PAS domain or for testing the effect of any ligand on any host cell's physiological process, wherein the process is mediated by any kinase having a PAS domain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Claims 1, 4, 6, and 7 are so broad as to encompass testing the effect of a ligand on the kinase activity of any protein with a PAS domain. Claims 8 and 9 are so broad as to encompass testing the effect of a ligand on any physiological process of any host cell, wherein the process is mediated by any kinase having a PAS domain. Claims 11, 12, 16, 17, 19, and 20 are so broad as to encompass testing the effect of a ligand on the kinase activity of any protein with the function of a PAS kinase. Claim 13, 14, and 18 are so broad as to encompass testing the effect of a ligand on any physiological process of any host cell, wherein the process is mediated by any protein with the function of a PAS kinase. The scope of each of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of methods broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired kinase activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification),

and detailed knowledge of the ways in which the protein's structure relates to its function. However, in this case the disclosure is limited to the PAS kinase set forth by GenBank Accession No. AF387103. Likewise, the specific reagents and steps used for methods to assay regulation of kinase activity or to assay regulation of a cellular process determines the method's success. Predictability of which steps and reagents can be used to successfully attain the desired objective of any method requires a knowledge of, and guidance with regard to how said steps and reagents relate to the desired objective. In this case the disclosure fails to provide guidance on any methods for testing the effect of ligand binding to the hydrophobic core of a PAS domain on either kinase activity or any cellular process. However, the art provides a method for testing the effect of ligand binding to the hydrophobic core of a PAS domain on kinase activity (Rutter et al, 2001; Figs 3 & 4) and on the cellular process of regulating glycogen synthase activity (Rutter et al, 2002; Fig 7).

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen any protein having multiple substitutions or multiple modifications for the desired PAS domain function, kinase activity, or PAS kinase activity, as encompassed by the instant claims. Furthermore, the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility limited in any protein and the results of such modifications are unpredictable (Wishart et al, 1995; Witkowski et al, 1999). Moreover, the amino acid sequences of known PAS domains do not show high levels of homology, thus sequence alignments provide little guidance as to the critical structural features that are necessary for the function of a PAS domain (Pellequer et al, 1999). One skilled in the art would expect any tolerance to modification for a given PAS domain-

containing protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of Claim 1, 4, 6, and 7, which encompasses any method for testing the effect of a ligand on the kinase activity of any protein with a PAS domain. The specification does not support the broad scope of Claims 8 and 9, which encompasses any method for testing the effect of a ligand on any cellular process, wherein the process is mediated by any kinase having a PAS domain. The specification does not support the broad scope of Claims 11, 12, 16, 17, 19, and 20, which encompasses any method for testing the effect of a ligand on the kinase activity of any protein with the function of a PAS kinase. The specification does not support the broad scope of Claims 13, 14, and 18, which encompasses any method for testing the effect of a ligand on any cellular process, wherein the process is mediated by any protein with the function of a PAS kinase. The specification does not support the broad scope of Claims 1, 4, 6-9, 11-14, and 16-20 because the specification does not establish: (A) regions of the protein structure which may be modified without effecting the function of (i) any PAS domain, (ii) any kinase having a PAS domain, or (iii) any protein with PAS kinase activity; (B) the general tolerance of the activity of any said proteins to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological function; (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices of proteins is likely to be successful in the recited methods; (E) any steps or reagents that may or may not be successfully used in methods for testing the effect of ligand binding to the PAS domain of a kinase on kinase activity or on any specific cellular process; (F) the general tolerance of any said

methods to modification and the extent of such tolerance; (G) a rational and predictable scheme for modifying any steps or reagents with an expectation of obtaining the desired objective of testing the effect of ligand binding to the PAS domain of a kinase on kinase activity or on any specific cellular process; (H) the specification provides insufficient guidance as to which of the essentially infinite possible choices of steps and reagents is likely to be successful in the recited methods.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including using any number of proteins in any number of methods, comprising any number of steps and/or reagents, wherein the method tests for the effect of ligand binding to the PAS domain of a kinase on either kinase activity or any cellular process. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of proteins and methods having the desired characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Written Description

Claims 1, 4, 6-9, 11-14, and 16-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the Inventors, at the time the application was filed, had possession of the claimed invention. These claims are directed to methods of using a genus of proteins having any structure wherein the protein is a kinase and has a PAS

domain with any structure. The specification teaches the structure of only a single representative species of such PAS domain-containing kinases. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of being a PAS domain-containing kinase. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 1, 4, 6-9, 11-14, and 16-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the Inventors, at the time the application was filed, had possession of the claimed invention. These claims are directed to a genus of methods for testing the effect of a ligand on (i) the kinase activity of a PAS domain-containing protein or (ii) a cellular process mediated by a PAS domain-containing kinase. The specification teaches no such methods and the prior art teaches only a single representative species of each of said methods. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4, 6, 7, 11, 12, 16, 17, 19, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by McKnight et al, 2001. McKnight et al teach a method for changing the binding specificity of the PAS-domain of PAS kinase by introducing a foreign ligand into the hydrophobic core of the PAS-domain, wherein the method measures a change in binding as a change in kinase activity (col 15, line 61- col 16, line 67). McKnight et al further teach a method for testing candidate drugs, wherein PAS kinase is expressed in host cells (col 3, lines 45-50). Therefore, Claims 1, 4, 6, 7, 11, 12, 16, 17, 19, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by McKnight et al, 2001.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8, 9, 13, 14, and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over McKnight et al, 2001. McKnight et al teach a method for detecting binding of ligands to the hydrophobic core of PAS kinase's

PAS-domain (col 14, line 54 – col 15, line 6). McKnight et al further teach a cellular method for assaying the effect of PAS kinase activity on cell growth (col 9, lines 14-43). McKnight et al do not disclose a specific method for detecting the effect of ligand binding to the hydrophobic core on cell growth. However, it would be obvious to a person of ordinary skill in the art to combine the two methods of McKnight et al et al, binding of ligand and measuring cell growth, to measure the effect of ligand binding on cell growth. To do so is suggested by McKnight et al, wherein they teach that the PAS domain of PAS kinase represents a valuable target for the identification of synthetic organic compounds capable of regulating the mitotic growth of mammalian cells (col 1, lines 41-50). The expectation of success is high, as McKnight et al teach methods for both binding of ligand and measuring cell growth.

This rejection is being made under 35 U.S.C. 102(b) and 35 U.S.C. 103(a) because, although McKnight et al do not teach the specific method recited in Claims 8, 9, 13, 14, and 18, they do teach all the steps and reagents of said method and predict the results of said method.

Claims 1, 4, 11, 12, 16, 17, 19, and 20 are rejected under 35 U.S.C. 102(a) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Amezcua et al, 2002. Amezcua et al teach a method for detecting binding of ligands to the hydrophobic core of PAS kinase's PAS-domain (Fig 4). Amezcua et al further teach the specific residues of said hydrophobic core that mediate binding (Fig 6D) and that said residues also regulate the intramolecular binding and modulation of kinase activity by the PAS domain (Fig 6B). Amezcua et al conclude that the ligand and kinase binding segments are functionally and structurally linked, suggesting a regulatory pathway for small organic compounds to regulate kinase activity in this system (pg 1349, parg 3). Amezcua et al teach methods for both binding

of ligand and for measuring kinase activity. Amezcua et al do not disclose a specific method for detecting the effect of ligand binding to the hydrophobic core on kinase activity. However, it would be obvious to a person of ordinary skill in the art to combine the two methods of Amezcua et al, binding of ligand and measuring kinase activity, to measure the effect of ligand binding on kinase activity. To do so is suggested by Amezcua et al, wherein they teach that there is a regulatory pathway for small organic compounds to regulate kinase activity in this system, as described above. The expectation of success is high, as Amezcua et al teach methods for both binding of ligand and measuring kinase activity.

This rejection is being made under 35 U.S.C. 102(a) and 35 U.S.C. 103 because, although Amezcua et al do not teach the specific method recited in Claims 1, 4, 11, 12, 16, 17, 19, and 20, they do teach all the steps and reagents of said method and predict the results of said method.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 11, 12, 16, 17, 19, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fejzo et al, 1999 in view of Rutter et al, 2001 and further in view of Rutter et al, 2002 or Katschinski et al, 2003 (see Exhibit A for public availability date). Fejzo et al teach an NMR-based method of screening libraries of organic compounds for binding to proteins (Figs 2 & 3). The organic compounds are derived from structures commonly found in known therapeutic agents (Fig 1). Fejzo et al do not teach screening their library of organic compounds

for binding to the PAS domain of PAS kinase or for regulation of kinase activity by said binding. Rutter et al teach the cloning of PAS kinase based its homology to the PAS domain of FixL, a heme-binding oxygen-sensing protein (pg 8992, parg 4). Rutter et al further teach that the PAS-A domain of PAS kinase is likely to incorporate a prosthetic group, in a manner similar to the PAS domain of FixL (pg 8996, parg 3). In fact, Rutter et al teach that their colleagues have demonstrated the ability of the PAS-A domain of PAS kinase to bind small synthetic chemicals in the region of the domain analogous to the heme-binding site of the FixL PAS domain (pg 8996, parg 4). It would have been obvious to a person of ordinary skill in the art to use the method of Fejzo et al to screen their library of ligands for binding to the PAS-A domain of PAS kinase and, furthermore, to test for regulation of kinase activity by said binding using the method of Rutter et al, 2001 (Figs 3 & 4). To do so is suggested by Rutter et al, 2001, wherein they state that the kinase activity of PAS kinase is likely to be regulated by ligand binding within the PAS domain (pg 8996, parg 4). Motivation to use the methods of Fejzo et al to test for regulation of PAS kinase activity by compounds that bind to the PAS domain derives from the desire to identify agents that modulate PAS kinase, which is known to be a regulator of sugar metabolism (Rutter et al, 2002; Katschinski et al, 2003). The expectation of success is high as, both methods for screening compounds for binding to proteins (Fejzo et al) and methods for measuring PAS kinase activity (Rutter et al, 2001) are known in the art. Therefore, Claims 1, 4, 11, 12, 16, 17, 19, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fejzo et al, 1999 in view of Rutter et al, 2001 and further in view of Rutter et al, 2002 or Katschinski et al, 2003.

Claims 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fejzo et al, 1999 in view of Rutter et al, 2001 and Strack et al, 2000 and further in view of Rutter et al,

2002 or Katschinski et al, 2003. As discussed above, the combination of Fejzo et al, Rutter et al, 2001, Rutter et al, 2002, and Katschinski et al, 2003 render obvious an in vitro method for regulating PAS kinase activity by binding an organic compound to the PAS domain. Said combination does not teach a cellular method for regulating PAS kinase activity by binding an organic compound to the PAS domain, wherein the PAS kinase in expressed by and within a host cell. Strack et al teach a method for expressing a kinase in a host cell and testing the effect of an organic compound to modulate phosphorylation by said kinase (Fig 3). It would have been obvious to a person of ordinary skill in the art to use the method of Strack et al to express PAS kinase in a host cell and test for the ability of the compounds of Fejzo et al to regulate kinase activity upon binding to the PAS domain. Motivation to do so derives from the desire to determine whether any of the organic compounds of Fejzo et al can regulate the activity of PAS kinase in an intact cell and, thereby, modulate the ability of PAS kinase to regulate sugar metabolism, as taught by Rutter et al, 2002 and Katschinski et al, 2003. The expectation of success is high, as methods of screening compounds for regulation of the activity of kinases expressed in host cells are known in the art. Therefore, Claims 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fejzo et al, 1999 in view of Rutter et al, 2001 and Strack et al, 2000 and further in view of Rutter et al, 2002 or Katschinski et al, 2003.

Claims 8, 9, 13, 14, 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rutter et al, 2002 in view of Fejzo et al, 1999 and further in view of Rutter et al, 2001 and Katschinski et al, 2003. The teachings of Fejzo et al, Rutter et al, 2002, Rutter et al, 2001, and Katschinski et al are described above. None of Fejzo et al, Rutter et al, 2002, Rutter et al, 2001, or Katschinski et al teach a cellular method for testing the effect of ligand binding to a PAS

domain on kinase activity, wherein kinase activity is detected by assaying regulation in a cellular process. Rutter et al, 2002 teach a cellular method for assaying the effect of PAS kinase activity on glycogen synthase (Fig 7). It would have been obvious to a person of ordinary skill in the art to use the method of Rutter et al, 2002 to screen the ligand library of Fejzo et al for an effect on on glycogen synthase activity of ligand binding to the PAS domain of PAS kinase. To do so is suggested by Rutter et al, 2001, wherein they state that the function of PAS kinase is likely to be regulated by ligand binding within the PAS domain (pg 8996, parg 4) and by Rutter et al, 2002, wherein they state that the PAS domain of PAS kinase is likely to sense a specific metabolic product whose abundance is reflective of ambient nutritional state (pg 25, parg 2). Motivation to use the method of Rutter et al, 2002 to test for PAS kinase-mediated regulation of glycogen synthase by the ligands within the library of Fejzo et al derives from the desire to identify agents that regulate glucose metabolism via PAS kinase, as taught by Rutter et al, 2002 or Katschinski et al, 2003. The expectation of success is high as, both methods for testing the role of PAS kinase on glycogen synthase and the library of organic compounds of Fejzo et al, which are derived from structures commonly found in known therapeutic agents, are known in the art. Therefore, Claims 8, 9, 13, 14, 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rutter et al, 2002 in view of Fejzo et al, 1999 and further in view of Rutter et al, 2001 and Katschinski et al, 2003.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Sheridan Swope

AV 1656

Exhibit A

Swope, Sheridan

From: Pilch, Susan (NIH/OD/ORS) [pilchs@ors.od.nih.gov]
Sent: Wednesday, June 29, 2005 3:20 PM
To: Swope, Sheridan
Subject: Mol Cell Biol article

Sheridan,

Targeted disruption of the mouse PAS domain serine/threonine kinase PASKIN.

Katschinski DM, Marti HH, Wagner KF, Shibata J, Eckhardt K, Martin F, Depping R,

Paasch U, Gassmann M, Ledermann B, Desbaillets I, Wenger RH.

Mol Cell Biol. 2003 Oct;23(19):6780-9.

The cited article appeared in volume 23, issue 19 of the journal *Molecular and Cellular Biology* in 2003. This issue was received by the NIH Library on September 25, 2003. The electronic full text of the article is freely available from the publisher; a pdf file of the article is attached:

<<6780.pdf>>

Susan M. Pilch, Ph.D., M.L.S.

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